Gene Expression Differences Identified in Skin Samples of Mycosis Fungoides, Atopic Dermatitis, and Psoriasis.

Aaron S. Farberg[1,2], Matthew S. Goldberg[3], Ann P. Quick[3], Olga Zolochevska[3], Christine N. Bailey[3], Jeff Wilkinson[3], Jonathan I. Silverberg[4], Peter A. Lio[5], John Koo[6], Jeffrey Weinberg[7], Mark Lebwohl[7]

1 – Baylor Scott & White Health System, Dallas, TX; 2 – Bare Dermatology, Dallas, TX; 3 – Castle Biosciences, Inc, Friendswood, TX; 4 – The George Washington University School of Medicine and Health Sciences, Washington, DC; 5 – Northwestern Feinberg School of Medicine, Chicago, IL; 6 – University of California San Francisco School of Medicine, San Francisco, CA; 7 – Icahn School of Medicine at Mount Sinai, New York, NY

Background

- Updates in the molecular understanding of common and often debilitating skin diseases such as atopic dermatitis (AD) and psoriasis (PSO) led to the development of multiple targeted systemic drugs.[1,2,3]
- Yet, molecular heterogeneity contributes to inconsistent clinical presentation and therapeutic response. Therefore, understanding a patient's personalized molecular profile may be important for determining the ideal therapy.[4,5]
- Further, systemic treatment of presumed AD or PSO can lead to delays in both diagnosis and proper treatment of patients with a true diagnosis of mycosis fungoides (MF) – a potentially dangerous clinical mimic of AD and PSO that requires a rigorous histologic and molecular workup to diagnose. [6,7]
- Therefore, a non-invasive method to distinguish molecular profiles of MF from AD and PSO could inform accurate diagnoses and avoid inappropriate treatment of MF.
- We have previously shown transcriptomic differences in AD and PSO samples obtained by a non-invasive scraping technique.[8] However, this technique has not been used to assess differences in gene expression profiles of MF samples.

Objective

- To identify gene expression differences based on diagnosis of MF, AD, or PSO and response to targeted systemic AD or PSO therapies.

Methods

- Lesional baseline samples were assessed from 76 patients (AD, n=24; PSO, n=48; and MF, n=4) enrolled in one of two IRB-approved studies (IDENTITY or SIGNAL-MF).
- The superficial epidermis was collected by gently scraping the skin ten times with a curette and immediately preserving in a proprietary buffer (Figure 1).

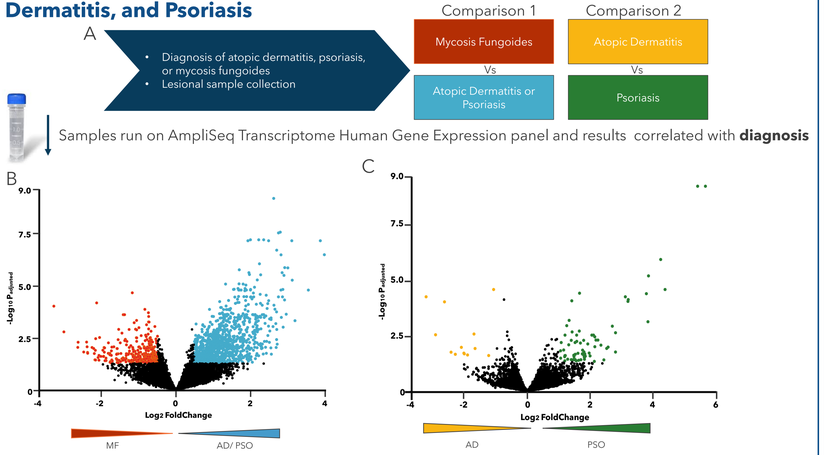
Figure 1. Non-invasive Scraping Method to Collect Atopic Dermatitis, Psoriasis, and Mycosis Fungoides Samples

1. Skin prep – clean with alcohol swab
2. Gentle scraping with curette 10 times
3. Quality check
4. Storage in RNA-preserving buffer

- Library preparation and next generation RNA sequencing were performed using the Ion AmpliSeq Transcriptome Human Gene Expression panel on the S5 Prime sequencer (ThermoFisher).
- Clinical response to a subset of AD patients taking dupilumab and PSO patients taking risankizumab was further assessed over 3 months using the eczema area and severity index (EASI) or psoriasis area or severity index (PASI), respectively.
- Gene expression was compared between MF, AD, and PSO. 1 chronic hand eczema sample and 1 psoriasis sample from a patient with concomitant eczema were excluded from diagnostic gene expression analysis. Further, gene expression was assessed based on response to therapy for the subset of AD patients taking dupilumab and PSO patients taking risankizumab with sufficient follow-up.
- Genes were considered significantly differentially expressed if there was a log2fold change >|1.0| and padj <.05.

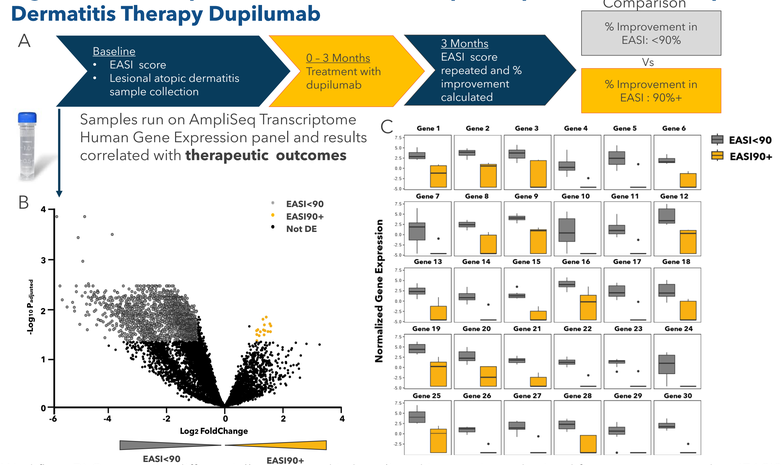
Results

Figure 2. Gene Expression Differences in Mycosis Fungoides, Atopic Dermatitis, and Psoriasis



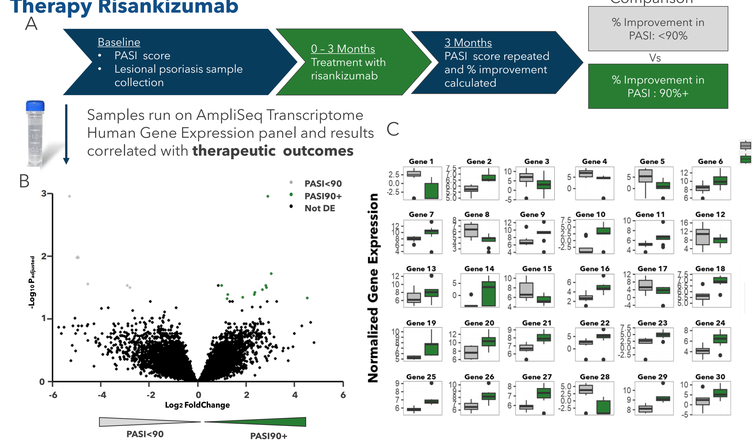
A) Workflow. **B**) Genes were differentially expressed in lesional skin samples from MF compared to PSO and AD. **C**) Differentially expressed genes in lesional skin samples from PSO compared to AD.
AD, atopic dermatitis; MF, mycosis fungoides, PSO, psoriasis.

Figure 3. Gene Expression Differences in Super-responders to the Atopic Dermatitis Therapy Dupilumab



A) Workflow. **B**) Genes were differentially expressed in baseline skin scrapings obtained from super-responders (EASI90+ response at 3 months, n=5) to dupilumab (blocks both IL-4 and IL-13 signaling) compared to those with EASI<90 (n=8) response. **C**) Top 30 differentially expressed gene distributions. *DE, significantly differentially expressed; EASI, eczema area and severity index; EASI90+, 90% or greater improvement in EASI; EASI<90, less than 90% improvement in EASI.*

Figure 4. Gene Expression Differences in Super-responders to the Psoriasis Therapy Risankizumab



A) Workflow. **B**) Genes were differentially expressed in baseline skin scrapings obtained from super-responders (PASI90+ response at 3 months, n=9) to risankizumab (blocks IL-23 signaling) compared to those with PASI<90 response (n=8). **C**) Top 30 differentially expressed gene distributions. *DE, significantly differentially expressed; PASI, psoriasis area and severity index; PASI90+, 90% or greater improvement in PASI; PASI<90, less than 90% improvement in PASI.*

Conclusions

- Robust gene expression is obtained from lesional PSO, AD, and MF samples collected by non-invasive skin scraping.
- Gene expression differences are observed between PSO, AD, and MF lesions.
- AD lesions from super-responders to dupilumab exhibit distinct gene expression.
- PSO lesions from super-responders to risankizumab exhibit distinct gene expression.
- A non-invasive molecular test is being developed to
  - Distinguish between AD, PSO, and MF.
  - Identify super-responders to AD and PSO therapies.

References

1. David E *et al.* Clin Exp Allergy. 2023;53(2):156-172.
2. Silverberg JI *et al.* J Eur Acad Dermatol Venereol. 2021; 35(9):1797-1810.
3. Armstrong A and Read C. JAMA. 2020;323(19):1945-1960.
4. Chovatiya R and Silverberg JI. JDD. 2022;22(2):172.
5. Mathur S and Sutton J. Biomed Rep. 2017; 7(1):3-5.
6. Lebas E *et al.* Dermatol Ther (Heidelb). 2021 11:1931–1951.
7. Espinosa ML *et al.* J Am Acad Dermatol. 2020 Jul; 83(1): 197–199.
8. Quick AP *et al.* BJD. 2023; 188(S3):420.

Disclosures & Acknowledgments

This study is sponsored by Castle Biosciences, Inc. ASF, JIS, PAL, JK, JMW, and ML are consultants for Castle Biosciences, Inc. APQ, MSG, OZ, CNB, and JW are employees and shareholders of Castle Biosciences, Inc.
Other disclosures: ASF, advisor (Sanofi and Regeneron, Janssen, Pfizer, Sun Pharma, BMS, Galderma, Novartis); JIS, advisor/consultant(Abbvie, Afyx, Aobiome, Arena, Asana, Aslan, BioMX, Biosion, Bluefin, Bodewell, Boehringer-Ingelheim, Cara, Castle Biosciences, Celgene, Connect Biopharma, Dermavant, Dermira, Dermtech, Eli Lilly, Galderma, GlaxoSmithKline, Incyte, Kiniksa, Leo Pharma, Luna, Menlo, Novartis, Optum, Pfizer, RAPT, Regeneron, Sanofi-Genzyme, Shaperon, Sidekick Health; speaker for Abbvie, Eli Lilly, Leo Pharma, Pfizer) and grants (Galderma, Pfizer); PAL, grants/funding(AbbVie, AOBiome, Eczema Foundation, National Eczema Association), speaker(AbbVie, Eli Lilly, Galderma, Hyphens Pharma, Incyte, La Roche-Posay/L'Oreal, MyOR Diagnostics, ParentMD, Pfizer, Pierre-Fabre Dermatologie, Regeneron/Sanofi Genzyme), consultant/advisor (AbbVie, Almirall, Amyris, Arbonne, ASLAN, Bodewell, Boston Skin Science, Bristol-Myers Squibb, Burt's Bees, Genzyme, Sibel Health, Skinfix, Sonica, Theraplex, UCB, Unilever, Verrica, Yobee Care; stock options with LearnSkin/Learn Health, Medable; Micreos, Modernizing Medicine, Yobee Care), patent pending(Theraplex product with royalties); board member/scientific advisory committee member (National Eczema Association); JK, speaker and/or consultant (AbbVie, Amgen, Celgene, Janssen, Eli Lilly, Leo Pharma, Novartis, Pfizer, UCB, Sun Pharma, Ortho Dermatologics, Regeneron, Sanofi, EPI Pharmaceuticals); JMW, speaker/ research grants (Regeneron, Abbvie, and Incyte), ML, research funds (Abbvie, Amgen, Arcutis, Avotres, Boehringer Ingelheim, Cara therapeutics, Dermavant Sciences, Eli Lilly, Incyte, Janssen Research & Development, LLC, Ortho Dermatologics, Regeneron, and UCB, Inc), consultant (Aditum Bio, Almirall, AltruBio Inc., AnaptysBio, Arcutis, Inc., Arena Pharmaceuticals, Aristea Therapeutics, Avotres Therapeutics, BiomX, Brickell Biotech, Boehringer-Ingelheim, Bristol-Myers Squibb, Cara Therapeutics, Castle Biosciences, Celltrion, Corevitas, Dermavant Sciences, Evommune, Inc., Facilitation of International Dermatology Education, Forte Biosciences, Foundation for Research and Education in Dermatology, Hexima Ltd, LEO Pharma, Meiji Seika Pharma, Mindera, Pfizer, Seanergy Trayi, and Verrica).